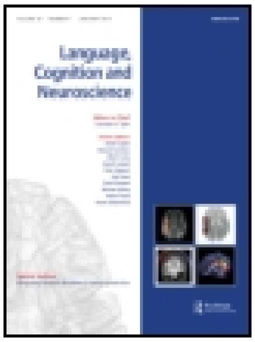

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What can functional Transcranial Doppler Ultrasonography tell us about spoken language understanding?

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ABSTRACT
This review describes language research conducted using the neurophysiological imaging technique, functional Transcranial Doppler Ultrasound (fTCD). FTCD estimates the blood flow velocity in the cerebral arteries from which, neural activity is inferred. The review provides a brief history and introduction to fTCD, including data acquisition, task design, and data processing. Challenges and solutions for the use of fTCD for language research are covered, reporting on production and comprehension paradigms, task difficulty and behavioural performance during covert and overt speech production, and participant characteristics (age and sex). We note the limited application of fTCD to the topic of spoken language understanding, commenting on the value of examining lateralisation in this endeavour, as well as the advantages of its use, namely portability and low cost, to supplement other imaging techniques.

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Speech; language; lateralisation; Doppler; functional Transcranial Doppler ultrasound

1. Historical background

Following the first reports of extracranial blood flow velocity (BFV) recordings using Doppler ultrasound (Miyazaki & Kato, 1965; Satomura & Kaneko, 1960), Aaslid, Markwalder, and Nornes et al. (1982) pioneered its use for intracranial blood vessels. They overcame the attenuative qualities of bone and soft tissues by using lower frequency ultrasound (1–2 MHz) and focusing on (or "insonating") vessels through the temporal bone windows – the thinnest skull region (see Figure 1(A)). In this way, BFVs were measured non-invasively in the middle, anterior, and posterior cerebral arteries (Aaslid et al., 1982), leading to widespread medical applications. More recently, researchers began to time-lock this activity to cognitive tasks – known as functional Transcranial Doppler Ultrasonography (fTCD) – taking unilateral (Droste, Harders, & Rastogi, 1989) and bilateral measurements (Hartje, Ringelstein, Kistinger, Fabianek, & Willmes, 1994; Rihs et al., 1995; Silvestrini, Cupini, Matteis, Troisi, & Caltagirone, 1994) with a goal of assessing cerebral lateralisation of cognitive abilities – relatively greater task-related activation of one hemisphere, compared to the other hemisphere. However, these early fTCD results with verbal and nonverbal tasks were ambiguous and lacked sufficient reliability to draw conclusions on an individual basis. Subsequent developments in experimental design (e.g. Knecht et al., 1996) and analysis (Deppe, Knecht, Henningsen, & Ringelstein, 1997), notably improved the sensitivity of fTCD and facilitated its use as a clinical and research tool for studying lateralisation.

Clinically, fTCD is used in pre-surgical evaluations of epilepsy patients (e.g. Knake et al., 2003), and in follow-up measurements with a range of patient populations (Knake et al., 2006), but studying language lateralisation is also of theoretical importance. A lateralised brain is thought to process information more efficiently (Rogers & Vallortigara, 2015; Vallortigara & Rogers, 2005), but associations are unclear in humans: atypical language lateralisation has not been associated with behavioural impairments in adults (Knecht et al., 2001). However, fTCD (Bishop, Holt, Whitehouse, & Groen, 2014; Illingworth & Bishop, 2009; Whitehouse & Bishop, 2009) and fMRI (Badcock, Bishop, Hardiman, Barry, & Watkins, 2012; de Guibert et al., 2011; Sun, Lee, & Kirby, 2010) research has repeatedly reported weaker language lateralisation to be more common in individuals with developmental language and literacy impairments. Bishop (2013; Bishop et al., 2014) discusses several possible explanations for this conundrum, but currently, the evidence is indecisive. Assessing language lateralisation directly (rather than relying on a behavioural proxy), in large samples of individuals varying in language proficiency and across development is needed to shed light on this issue, and fTCD is a fitting technique in this endeavour.

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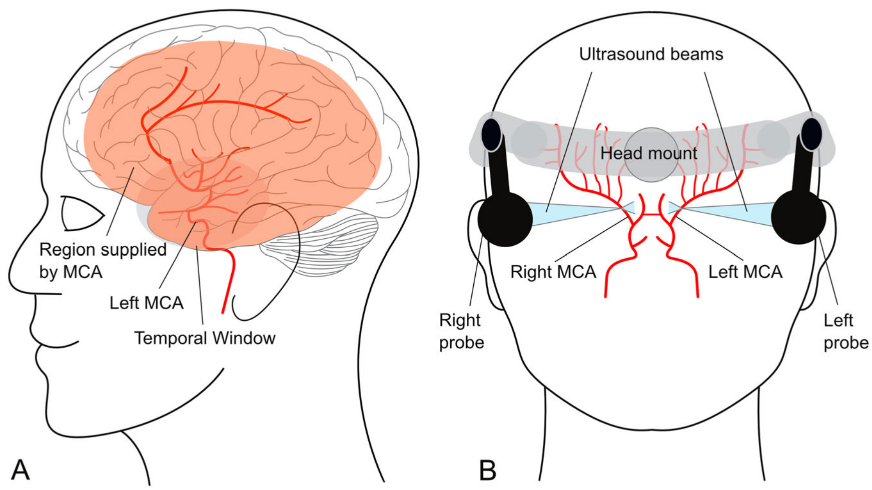

Figure 1. Panel A: A cartoon diagram of the left temporal window, underlying middle cerebral artery (MCA), and region supplied by MCA. Panel B: Example insonation of the left and right middle cerebral arteries, including the headmount with the probes fitted. Please note this is for illustration purposes only. For photographs and diagrams of the variability of temporal windows see Ringelstein, Kahlscheuer, Niggemeyer, and Otis (1990). There is also a free interactive simulator that provides clear diagrams (available for Windows operating systems from Haemodynamics AG, http://www.transcranial.com/edu/download.html).

2. Overview of the method

2.1. The neurophysiology of fTCD

Via insonating a blood vessel through the temporal bone windows of the skull (i.e. transcranially; see Figure 1), BFV (cm/s) can be determined be comparing frequency changes of the transmitted and returned ultrasound signals reflected against the moving blood cells (i.e. the well-known Doppler effect). As cerebral BFV increases in response to neural firing in order to maintain resources to the cells (Escartin & Rouach, 2013; Li & Freeman, 2015; Villringer & Dirnagl, 1995), neural activity in the brain regions supplied by the insonated vessel can be inferred. The middle cerebral artery (MCA) is the most commonly insonated vessel in language research, supplying blood to approximately 50% of the cortex (van der Zwan, Hillen, Tulleken, & Dujovny, 1993), including areas linked to language processing (see Table 1). Therefore, when someone produces speech, there will be an accompanying increase in BFV in the MCA which can be measured using fTCD. See Bishop, Badcock, and Holt (2010) for a video demonstration of the procedure and Figure 2 for its relation to other neurophysiological methods.

2.2. Data acquisition

An experienced user can insonate vessels in less than 5 minutes but the location is variable and, as a result, setup time can be longer (for a setup guide, including depth of insonation, see Badcock, Spooner, et al., 2016). One caveat to the fTCD procedure is that insonation of a vessel may fail in 5–10% of people (in the authors' experiences and given in Lohmann, Ringelstein, & Knecht, 2006), 9% of children (0–16 years, Iova et al., 2004), and up to 25% in older adults (i.e. 55-years and over: M = 71; Bakker et al., 2004). Failure is due to the thickness and density of the temporal bone window, which tends to affect women (i.e. thicker) and older adults (i.e. less density leads to greater signal refraction) with higher likelihood (Wijnhoud, Franckena, van der Lugt, Koudstaal, & Dippel, 2008); medication also affects bone thickness (Kattan, 1970; Lefebvre, Haining, & Labbé, 1972). Once setup, session duration is task dependent, typically requiring between 30 and 60 seconds per trial. Although not systematically investigated (but see Badcock, Spooner, et al., 2016, for reliability at varying numbers of trials), typical studies include 20 or more trials, lasting between 10 and 20 minutes.

2.3. Task design

With regard to language research, fTCD has mainly been used to study lateralisation. Bilateral monitoring makes it particularly suited to this purpose. To illustrate the key variables, we focus on the gold standard language lateralisation task in fTCD research: word generation. For this task, participants are asked to silently generate words beginning with a visually presented letter (see Figure 3). This is preceded by a 5-seconds preparatory period with a "Clear Mind" instruction. Words are generated for 15 seconds, followed by a 5-second period of overt report to ascertain task compliance. A 35-second

Table 1. Description of the cortical coverage and relevance for language (from Price, 2010) of brain regions supplied by the left middle cerebral artery. The coverage is based upon examination of 50 hemispheres from 25 post-mortem brains, and the description is minimally adapted from Gibo, Carver, Rhoton, Lenkey, and Mitchell (1981).

Lobe	Coverage	Gyrus	Brodmann area	Relevance for language
Frontal	Lateral half of the orbital surface and the area between the Sylvian fissure below, the superior frontal sulcus with frequent overlap onto the superior frontal gyrus above, and the central sulcus posteriorly and near, but stopping short of the frontal tip anteriorly. The branches of the MCA did not reach the superior margin nor the medial surface	Pars orbitalis	47	Semantic retrieval processes
		Pars triangularis	45	Word selection (comprehension and production)
		Pars opercularis	44	Hierarchical sequencing and articulatory planning
		Middle frontal	46	Word retrieval (more in production)
		Precentral	6, 4	Initiation and execution of movement Sensorimotor interface
Parietal	Bounded anteriorly by the central sulcus, inferiorly by the Sylvian fissure, and superiorly by the inferior half of the superior parietal lobule. Posteriorly, the area extended backward onto the lateral surface of the occipital lobe	Postcentral	3, 1, 2	Phonological retrieval/covert articulation Semantic constraints
		Inferior and superior parietal lobules (including the supramarginal and angular gyri)	40, 39	
Temporal	Entire lateral surface except for a small posteroinferior strip. In addition, it supplied the lateral part of the inferior surface of the temporal lobe, the temporal pole, the uncus, and adjacent part of the parahippocampal gyrus. Branches frequently extended onto the lateral surface of the occipital lobe	Superior temporal (including Heschl's gyrus and the Planum Temporale)	41, 42, 22	Auditory input Prelexical auditory objects Sensorimotor integration
		Middle temporal	21	Semantic processing of single words
		Inferior temporal	20	Amodal semantic combinations
		Temporal pole	38	Intelligible speech/amodal semantic combinations
Occipital	Branches supplying the parietal and temporal lobes overlapped onto the lateral occipital gyri, but they did not extend to the occipital pole	Lateral occipital gyri	19	

period of relaxation follows to return BFV to a resting state (i.e. normalisation): a baseline against which activation can be compared. Each trial lasts for 60 seconds. The task, pioneered by Knecht et al. (1996), is reliable (Knecht, Deppe, Ringelstein, et al., 1998), and has been validated against the Wada technique (Knecht, Deppe, Ebner, et al., 1998) and fMRI (Deppe et al., 2000; Somers et al., 2011). These comparisons, as well as its extensive use in the literature, set word generation as a standard paradigm for fTCD research.

The required elements of fTCD paradigms include normalisation/baseline, preparation, and activation. Normalisation should be included before and after an event to ensure that activity is sufficiently separated from adjacent events. However, normalisation duration varies between studies. Gutierrez-Sigut, Payne, and MacSweeney (2015) used a 10-second normalisation, whereas Badcock, Nye, and Bishop (2012) used 25 seconds. Despite Gutierrez-Sigut et al. and Badcock et al. reporting typical distributions of lateralisation, the task reliability was low (split-half $r = 0.61$ and Cronbach's $\alpha = 0.52$, respectively) compared with canonical replications of word generation (e.g. $r = 0.89$; Bishop, Watt, & Papadatou-Pastou, 2009). Although likely that some minimum is required, this has not been investigated. Alternative strategies to the "relax" normalisation have been implemented, for example, watching a to-be-described video (i.e. animation description; Bishop et al., 2009) which is more engaging for children and reported to result in non-lateralised activity. This may be useful for lateralisation research but for other applications, especially with adults, less engaging normalisation may be best.

Task preparation is cued by a brief tone usually accompanied by "Clear Mind" text presented for 5 seconds. The presence of the tone has been demonstrated to increase the magnitude of the change in BFV in the predicted direction; that is, greater left velocity for word generation (Knecht et al., 1996); though again, the text instruction has not been investigated.

Activation is cued by the presentation of a letter to which participants are instructed to silently generate words. Silent generation of words was originally encouraged to avoid movement artefacts, however, overt tasks have been successfully employed without issue (e.g. Gutierrez-Sigut, Payne, et al., 2015). The early work encouraged the production of four words per letter (Knecht et al., 1996), later adjusted to "as many as you can" (Knecht, Deppe, Ebner et al., 1998). Presumably this extension results in greater activation consistency between trials and therefore internal reliability, although this has not been tested.

The duration of normalisation and activation periods allows time for change in BFV to plateau (i.e. approximately 10 seconds; Rosengarten, Osthaus, & Kaps, 2002); however, the required time is derived from a paradigm without a preparation period. As noted by Knecht

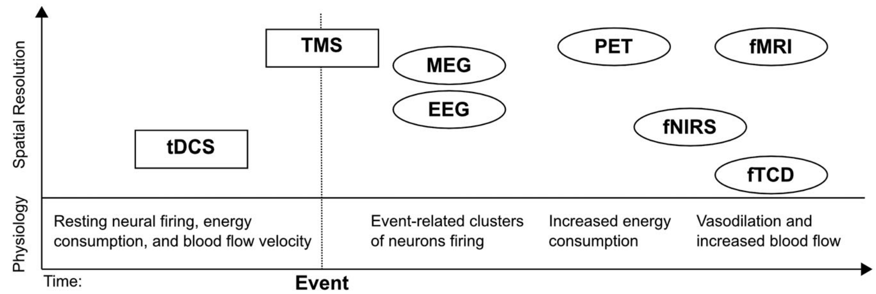

Figure 2. Schematic of the spatial resolution and temporal relationship between active (squares) and passive (ovals) neurophysiological methods and physiological activity (Deppe, Ringelstein, & Knecht, 2004; Walsh & Cowey, 2000). Methods: transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), magnoencephalography (MEG), electroencephalography (EEG), positron emission tomomography (PET), functional near infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI), functional Transcranial Doppler Ultrasound (fTCD).

et al. (1996), peak change following cuing occurs at around 4 seconds. Shorter activation periods have been used; for example, single word report in less than 5 seconds to brief (3 to 5 word) definitions (Badcock, Nye, et al., 2012). Although the lateralisation results were comparable to word generation, the relationship between the two tasks was weak. Further investigation to determine optimal task parameters is warranted.

It is worth noting that fTCD language research uses blocked designs, in contrast to rapid event-related designs used with fMRI (D'Esposito, Zarahn, & Aguirre, 1999) or EEG (i.e. event-related potentials; Luck, 2014). Theoretically, rapid event-related fTCD designs are possible, however, to our knowledge, this has not been tested.

2.4. Data processing and analysis

FTCD data are processed in a number of steps to calculate event-related change in BFV (see Table 2 and Deppe, Knecht, Lohmann, & Ringelstein, 2004; Deppe et al., 1997, for further details). Example group data for word generation are displayed in Figure 3. Critically, the difference between the left and right velocities shows an increase from 5 to 15 seconds, indicating left lateralisation at the group level. Whilst the primary purpose of the documented processing is for laterality index calculation (see Table 2), the timing and amplitude of left-right average, left and right independent (e.g. in a vigilance experiment, Schultz, Matthews, Warm, & Washburn, 2009), or single channel changes in velocity may address new questions.

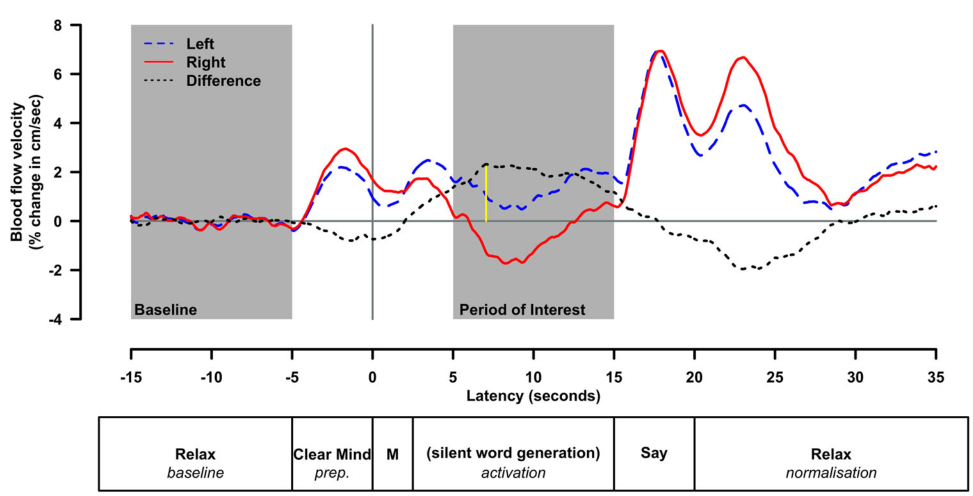

Figure 3. Blood flow velocity (% change in cm/s) to silent word generation (a latency of 0 corresponds to letter presentation to cue generation). Mean activity for a group ($n = 17$) are presented for the left and right middle cerebral arteries, and the left minus right difference. Baseline and period of interest timings are marked, along with the peak difference (vertical bar within the period of interest). A schematic of the task elements is displayed below the *x*-axis, including a period of relaxation to establish baseline blood flow velocity, a preparatory cue to "Clear Mind", a letter stimulus to cue silent word generation beginning with the presented letter, a period of silent word generation, followed by overt report of the words (i.e. "Say"), and then relaxation to induce normalisation of blood flow velocity. The laterality index is 2.07% change from baseline [95% confidence intervals: 1.99, 2.14].

Table 2. Summary of processing and analysis steps for fTCD data (for further details see Deppe et al., 1997).

Step	Description	Comment
Downsampling	Data are usually recorded at 100 Hz and downsampled to 25 Hz (1 sample every 40 ms)	Historically this step was required as computing power was limited, in addition to the fact that the blood flow response is slow so millisecond accuracy is overkill. Given the power of modern computers, this step may be skipped, however, downsampling will increase the speed of processing
Normalisation	Data for each channel are transformed to have a mean of 100	The angle of the ultrasound probe will likely differ between left and right channels, resulting in differences in overall velocity. Normalisation corrects for this difference. This removes any intra-individual differences as well resting state differences between channels
Heart Cycle Integration	Fluctuations in velocity due to the heart cycle (i.e. pulse) are removed by averaging across individual cycles	This is a form a data cleaning that does not introduce artefacts associated with bandpass filtering and improves the frequency distribution of the data (from bimodal to unimodal), rendering it suitable for traditional statistical interrogation. See Pinaya et al. (2015) where this is not included and Badcock, Pascoe, and Groen (2016) for a response to this
Epoching	The continuous recording is divided into event-related time periods	
Data Screening	Epochs with extreme values are excluded from further analysis	Extreme data is considered a recording artefact, often due to probe displacement caused by movement. This can be identified as a) values beyond a certain range (e.g. ±50 cm/s beyond the mean of the data) or b) a channel difference outside the expected range (e.g. 20 cm/s where the average is usually less than 5 cm/s)
Baseline Correction	Subtraction of average activity during a control period from all data within an epoch, for the left and right channels separately	Requires the specification of a baseline time period within the epoch, during which rest or control-task activity is assumed. The percentage change in activation due to the task can be inferred. Periods of 4 to 10 seconds have been used in the literature (10 in Bishop et al., 2009; in Gutierrez-Sigut, Daws, et al., 2015) – the effects have not been compared systematically
Laterality Index Calculation	The peak left minus right channel activation difference within a period of interest is determined. The average activation within a 2-second time-window around this peak is the laterality index	The period of interest is selected in relation to task-onset – typically with a 5-second delay to allow velocity to peak. Left activation is reflected by positive values, right is negative

Deppe and colleagues developed the processing steps, easily implemented with their software Average (described in Deppe et al., 1997, 2004). Average is Windows-based software, and a cross-platform implementation of the methods is available with the MATLAB toolbox, dopOSCCI (introduced in Badcock, Holt, Holden, & Bishop, 2012). The toolbox allows for customisation and extension to the steps, and introduced activation correction for extreme values as well as rejection of extreme values based on the left minus right difference (see Badcock, Spooner, et al., 2016).

At the individual level, changes in BFV have been analysed using comparison of indices to zero using 95% confidence intervals (e.g. Groen, Whitehouse, Badcock, & Bishop, 2013) and analyses of variance (e.g. Badcock, Nye, et al., 2012).

3. Challenges and solutions for studying spoken language

With the focus of fTCD language research on lateralisation and its potential use as a clinical tool in epilepsy surgery, common language tasks for fTCD require the production of words (e.g. word generation, naming) or sentences (e.g. sentence construction, picture, or animation description). Although tasks vary in terms of the amount of auditory input and comprehension demands, few studies have investigated understanding of spoken language per se. In the following sections, we discuss existing use of receptive language tasks in fTCD research, and how fTCD responses to language tasks are associated with task difficulty and performance, and participant characteristics.

3.1. Types of language tasks

Research has compared comprehension and language production using listening to short stories (jokes, poems, or everyday life events) versus producing short stories from a picture cue (Stroobant, Van Boxstael, & Vingerhoets, 2011), and sentence judgements versus word generation (Buchinger et al., 2000). Consistent with work using the Wada technique (e.g. Boatman et al., 1998) and fMRI (e.g. Tzourio-Mazoyer, Josse, Crivello, & Mazoyer, 2004), receptive tasks are less strongly lateralised than expressive tasks (Buchinger et al., 2000; Stroobant et al., 2011). However, the expressive and receptive tasks in this research were poorly matched for auditory input or linguistic content, therefore lateralisation differences could be due to increased bilateral involvement in multiple processes (e.g. phonological, syntactic, or semantic knowledge). In a comparison of listening to stories versus noise or melody, Carod Artal, Vazquez Cabrera, and Horan (2004) reported a larger increase in left lateralisation to stories. In this case, stimulus complexity varied between conditions, complicating interpretation of the results. Although most fTCD work has investigated lateralisation for language as if language were a unidimensional construct, Gutierrez-Sigut, Daws, et al. (2015, 2015) compared the traditional word generation task (i.e. phonological fluency) with a semantic fluency equivalent and did not find differences in direction or degree in lateralisation indices. In contrast, Stroobant, Buijs, and Vingerhoets (2009) compared tasks tapping multiple linguistic processes and found stronger left lateralisation for tasks involving word generation (phonological fluency) or syntactic processes (sentence construction) than one involving semantic (synonimity) judgements.

To date, fTCD has been used for relatively crude categorisation in tasks with high ecological validity, but poor on experimental control, and which mostly conceptualise language as a unidimensional construct. To increase our understanding of lateralisation of language – and the utility of fTCD to study it – it is important to address the following issues. Firstly, experimental control over a range of factors (e.g. task difficulty) that influence lateralisation is poor. Secondly, lateralisation for language is predominantly treated as a unidimensional construct, however, as illustrated by Stroobant et al. (2009), degree of lateralisation can vary between language tasks. It remains an outstanding question whether a single laterality measure is suitable to summarise activity across tasks, or whether individual variation between language tasks is meaningful. Carefully matching task properties tapping different linguistic domains and processes in both production and comprehension, and recognising individual differences between these domains are important next steps.

3.2. Associations with task difficulty and performance

Task difficulty is one parameter that might influence fTCD-estimated lateralisation, but results have been inconsistent. Dräger and Knecht (2002) manipulated the difficultly of word generation by providing participants with letters forming the beginnings of words, contrasting the frequency of available items (i.e. high = easy, versus low = hard). Although behavioural accuracy matched retrieval difficulty, fTCD outcomes did not: consistent with other fTCD work with language (Badcock, Nye, et al., 2012) and spatial ability (Rosch, Bishop, & Badcock, 2012). In an fMRI follow-up, Dräger et al. (2004) suggested that lack of suitable cerebral territory supplied by the MCA rendered fTCD insensitive to their difficulty manipulation: parietal regions outside this territory were highlighted. However, recently, pace of decision-making was evident using fTCD. Payne, Gutierrez-Sigut, Subik, Woll, and MacSweeney (2015) manipulated the number of word-pair rhyme and line orientation judgments required in a 17.5-second period: 5 or 10. More judgments were associated with stronger lateralisation for rhyme (greater left) and line (greater right) tasks. Therefore, fTCD is sensitive to some aspects of task difficulty.

The behaviour-lateralisation relationship is important for interpreting silent word generation tasks comparing groups that may differ in language abilities (e.g. dyslexia, Illingworth & Bishop, 2009). In such studies, it is impossible to establish whether the behavioural differences underpin neural differences – this concern is supported by a lack of relationship between the number of words reported and fTCD measurements in word generation (Badcock, Nye, et al., 2012). However, Gutierrez-Sigut, Payne, et al. (2015) have demonstrated similar activation for covert and overt speech, observing a significant correlation between behaviour and fTCD lateralisation for overt speech. Therefore, overt speech paradigms are recommended.

3.3. Associations with participant characteristics

Lateralisation is also influenced by participant characteristics, such as age, sex or, relatedly, menstrual cycle. Regarding age, one fTCD study in children (1–5 years) reported greater left lateralisation at younger ages (Kohler et al., 2015); however, the majority (ages ranging from 2 to 16) report no association (Groen, Whitehouse, Badcock, & Bishop, 2012; Haag et al., 2010; Hodgson, Hirst, & Hudson, 2016; Lohmann, Dräger, Müller-Ehrenberg, Deppe, & Knecht, 2005; Stroobant et al., 2011) which is at odds with fMRI (Gaillard et al., 2000; Holland et al., 2001, 2007; Szaflarski, Schmithorst, et al., 2006; Szaflarski, Holland, Schmithorst, & Byars, 2006). This discrepancy could be explained by greater sensitivity in fMRI to area-specific age-related changes or by the fTCD tasks used. As Holland et al. (2007) suggested, assessing late-acquired language skills may result in age-related differences in lateralisation, but the fTCD tasks typically require description of simple pictures or animation, probing early-acquired skills. At the other end of the spectrum, older participants showed reduced left-lateralised activation during a word generation task (60–75 year-olds, Keage et al., 2015).

Concerning sex,[1] despite a long-standing debate on male–female language lateralisation differences, empirical support for more bilateral language in women is lacking (Sommer, Aleman, Bouma, & Kahn, 2004; Sommer, Aleman, Somers, Boks, & Kahn, 2008), or effects are very small, and possibly age-dependent (Hirnstein, Westerhausen, Korsnes, & Hugdahl, 2013). This is in line with a lack of sex differences reported in fTCD studies (e.g. Knecht et al., 2000; Whitehouse & Bishop, 2009). Interestingly, a recent study evaluating the test–retest reliability of lateralisation using fTCD across several weeks, found laterality indices were much more variable in women (Helmstaedter, Jockwitz, & Witt, 2015); specifically, a relative shift towards bilateral activation in women at menstrual cycle onset. This finding demands consideration of menstrual cycle when assessing lateralisation and it may explain contrasting findings on sex differences, and confound existing between group research. Therefore, both age and sex are important factors in lateralisation research and may be important for fTCD research per se.

4. Advantages and future directions

Language research with fTCD is in its infancy, predominantly applied in clinical settings, using ecologically valid, but poorly controlled paradigms, probing multiple aspects of language simultaneously. As such, there are no key empirical contributions to the understanding of spoken language yet. Nevertheless, fTCD is worth consideration as the field is ripe for paradigm development and refinements in analysis, including considering measures beyond laterality indices. These developments enable the advancements of our understanding of language lateralisation for production and comprehension.

4.1. Advantages of fTCD

Although its spatial resolution is limited (see Figure 2 and Table 1), fTCD has several advantages, compared to other techniques. It is highly portable and relatively inexpensive (Pelletier, Sauerwein, Lepore, Saint-Amour, & Lassonde, 2007), making it a useful screening tool for investigations requiring large sample-sizes, such as genetic studies (e.g. Somers et al., 2015). Additionally, its robustness to articulation and gross movements, and participant friendly administration, make it well suited for use with young children, older adults, and patient groups. Indeed, adaptations of the gold standard word generation task eliciting overt sentence production in response to pictures (Haag et al., 2010; Lohmann et al., 2005) or animations (Bishop et al., 2009) or picture naming (Badcock et al., 2016; Kohler et al., 2015) have resulted in reliable measurements of language lateralisation. Moreover, the nature of the ultrasound signal makes it appropriate for research where other techniques are not, such as in individuals with cochlear implants (e.g. Chilosi et al., 2014). As fTCD is non-invasive and can be administered repeatedly in the same participants, there are opportunities to examine and project recovery from stroke (for e.g. in motor control see Sarkar, Ghosh, Ghosh, & Collier, 2007). The advantages of fTCD – low-cost, portability, robustness to articulation and gross movements, and participant friendly administration – support its use as an imaging technique for language research in the foreseeable future, supplementing weaknesses of other techniques.

4.2. Future developments in task design and data analysis

As mentioned, there are a number of task parameters yet to be optimised for fTCD. This concerns all phases of a trial: normalisation, preparation, and activation (see Section 2.3). There are outstanding questions regarding the influence of task instruction on preparation and behaviour. Also, the number of required trials and the possibility of adopting a rapid event-related (instead of a blocked) design, merit investigation. Refining matching of stimulus properties across conditions to equate demands between production and comprehension tasks is needed to investigate whether a unidimensional view of language lateralisation is justified. Regarding analysis, we are yet to optimise data cleaning techniques to maximise the signal to noise ratio (Badcock, Spooner, et al., 2016) and variables beyond the peak difference should be considered (e.g. trajectory of BFV increase to infer neural substrates; Meyer, Spray, Fairlie, & Uomini, 2014). Following a different approach, resting TCD can be used to investigate cerebrovascular functioning (Keage et al., 2012). This approach has associated poorer cerebrovascular functioning to decreased fluid, but not crystallised, intelligence in aging populations (Keage et al., 2015). These developments offer exciting potential for the use of fTCD for the investigation of spoken language.

Note

1. Here, we refer to the dichotomous variable sex. We note that the continuous variable of hormones levels will likely be the more accurate advancement for this research (e.g. Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Güntürkün, 2000).

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